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Relations of hepatic steatosis with liver functions, inflammations, glucolipid metabolism in chronic hepatitis B patients

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Abstract. – OBJECTIVE: To investigate the relations between the steatosis and liver functions, inflammations, and glucolipid metabolism in chronic hepatitis B patients.

PATIENTS AND METHODS: A total of 144 chronic hepatitis B patients who were admitted to our hospital from January 2015 to April 2017 were selected and divided into the steatosis group (n=73) and the non-steatosis group (n=71) according to the detection of hepatic puncture biopsy. The general information of the patients including age, sex, and body mass index (BMI) was collected, and patients' liver functions, inflammations, and glucolipid metabolism indicators were determined and compared between the chronic hepatitis patients with steatosis and without steatosis. The chronic hepatitis patients with steatosis were further divided into the normal group and the abnormal group based on the level of C-reactive protein (CRP) (8 mg/L). Besides, according to the level of aspartate aminotransferase (AST), these patients were divided into the normal liver function group (AST<40 U/L) and the abnormal liver function group (AST>40 U/L), among whom the hepatic steatosis, glucolipid metabolism, and inflammations were compared. At the same time, the chronic hepatitis B patients with steatosis were divided into Group F1, Group F2, and Group F3 based on the fatty degeneration grade, the correlations of steatosis with inflammations, glucolipid metabolism, and liver functions were analyzed. At last, the regression analyses between steatosis and the inflammation grade, glucolipid metabolism and liver function indicators were conducted for Group F1, F2, and F3, respectively.

RESULTS: In the chronic hepatitis B patients with steatosis, liver function indicators-alanine aminotransferase (ALT) and AST, levels of inflammatory factors-interleukin-2 (IL-2), IL-6 and CRP and glucolipid metabolism indicators-fasting blood glucose (FBG), 2h postprandial blood glucose (2h PBG), fasting insulin (FINS), triacylglycerol (TG), total cholesterol (TC), and low-density lipoprotein (LDL) were significantly higher than those without steatosis ($p<0.05$). The steatosis, liver functions, and glucolipid metabolism indicators were statistically different between patients in the normal inflammatory factor group and the abnormal inflammatory factor group ($p<0.06$). In addition, the liver function indicators (ALT and AST) and glucolipid metabolism indicators (FBG, 2h PBG, FINS, TG, TC, HDL, and LDL) in the abnormal group were statistically higher than those of normal inflammatory factor group ($p<0.05$). In the normal liver function group, the average fatty degeneration grade was statistically lower than that in the abnormal liver function group ($p<0.05$), and glucolipid metabolism indicators (FBG, 2h PBG, FINS, TG, TC, IL-2, IL-6, CRP, HDL, and LDL) were also markedly lower than those in the abnormal liver function group ($p<0.05$). The steatosis was positively correlated with relevant indicators, including the blood glucose indicator of FBG ($r=0.509$, $p<0.05$), liver function indicator of AST ($r=0.602$, $p<0.05$), the blood lipid indicator of TG ($r=0.740$, $p<0.05$), and the inflammatory factor of CRP ($r=0.882$, $p<0.05$), respectively. The disease course, BMI, 2h FBG, FINS, TG, TC, HDL, LDL, AST, ALT, and inflammatory factors of IL-2, IL-6, and CRP were involved in risk factors of steatosis ($p<0.05$).

CONCLUSIONS: Our data demonstrates that the steatosis is correlated with liver functions, glucolipid metabolism and inflammation level in chronic hepatitis B patients, and the foregoing indicators can affect the disease development of chronic hepatitis B patients with steatosis.

Key Words

Chronic hepatitis B, Steatosis, Liver functions, Inflammations, Glucolipid metabolism.

Introduction

Currently, the statistical findings have shown that there is an increasing incidence rate of chronic hepatitis B in China, which occurs followed by the inflammations and glucolipid metabolism disorder, causing inconvenience in the daily life

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of patients[1-3]. The previous evidence[4-6] implied the relations between steatosis and liver functions, inflammations, and glucolipid metabolism in hepatitis B patients. Fasting has an impact on the inflammatory state, as well as metabolic and anthropometric parameters[7]. In addition, parameters such as body mass index (BMI), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), glutamic-pyruvic aminotransferase (ALT), glutamic-oxalacetic aminotransferase (AST), fasting plasma glucose (FPG), fasting insulin (FINS) were considered as risk factors in non-alcoholic fatty liver disease, a type of chronic liver disease[8]. In this study, we aimed to evaluate the indicators in the chronic hepatitis B patients with steatosis based on clinical data.

Patients and Methods

General Information

A total of 144 chronic hepatitis B patients admitted to our hospital from January 2015 to April 2017 were enrolled, and the hepatic puncture biopsy indicated that there were 73 patients combined with steatosis and 71 patients without steatosis. The age of all patients was 30-65 years old with the average age of (43.43±6.54) years old. All patients were informed of the study scheme prior to the study and signed the informed consent.

Inclusion criteria: patients detected with the positive hepatitis B virus-deoxyribose nucleic acid (HBV-DNA), with an elevation of alanine aminotransferase (ALT) via serum determination and with hepatitis lesions via liver histopathologic assay.

Methods

The liver functions, glucolipid metabolism, and inflammatory factors were compared between chronic hepatitis B patients with steatosis and without steatosis.

According to the level of C-reactive protein (CRP) (8 mg/L), the chronic hepatitis B patients were divided into the normal group and the abnormal group.

Based on the level of aspartate aminotransferase (AST), the chronic hepatitis B patients were divided into the normal liver function group (AST<40 U/L) and the abnormal liver function group (AST>40 U/L), and their steatosis, glucolipid metabolism, and inflammations were compared.

The correlations of fatty degeneration grade with the inflammation, glucolipid metabolism, and liver function indicators were analyzed for chronic hepatitis B patients combined with steatosis.

The regression analyses between the steatosis, inflammation grade, glucolipid metabolism, and liver function indicators were performed for the chronic hepatitis B patients with steatosis.

Observation Indicators

Fatty degeneration grade: patients with less than 30% liver cells presenting steatosis in hepatic lobules were regarded as F1, patients with 30%-50% liver cells presenting steatosis as F2, patients with 50%-75% liver cells presenting steatosis as F3.

Venous blood samples were drawn to determine levels of fasting blood glucose (FBG), 2h postprandial blood glucose (2h PBG), fasting insulin (FINS), triacylglycerol (TG), total cholesterol (TC), high-density lipoprotein (HDL), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and low-density lipoprotein (LDL) by using automatic biochemical analyser. IL-2 and IL-6 were tested using the ELISA kit from Keygen Biotechnology (Nanjing, China), and CRP was measured by using ELISA kit produced by Beyotime Biotechnology (Hangzhou, China) following the instructions of the manufacturer. Plates were read at 450 nm using a microplate reader (Multiscan MS™, Labsystems, Helsinki, Finland). The primary concentration of each test sample was calculated from the linear regression equation based on the OD values of the standards[9].

Data Processing and Analysis

All test results were summarized and analyzed by SPSS17.0 software (SPSS Inc., Chicago, IL, USA). The measurement data were expressed as ($\bar{x} \pm s$), and the inter-group differences were analyzed by *t*-test. The enumeration data were represented as n, and the inter-group differences were verified via chi-square test. $p<0.05$ presented statistical differences.

Results

Comparisons of Liver Functions, Inflammations, and Glucolipid Metabolism Indicators Between Two Groups of Patients

The liver function indicators (ALT and AST), inflammatory factors, and glucolipid metabolism indicators (FBG, 2h PBG, FINS, TG, TC, HDL, and LDL) were compared between patients from

Table I. Comparisons of liver functions, inflammations and glucolipid metabolism indicators between two groups of patients.

Items	Chronic hepatitis B patients with steatosis	Chronic hepatitis B patients without steatosis	*t*	X^2	*p*
Age (years)	38.21±3.21	37.98±3.01	0.44		0.65
Gender (male/female)	34:39	30:41		0.27	>0.05
Course of disease (years)	5.21±0.45	5.11±0.32	1.53		0.13
FBG (mmol/l)	5.9±0.4	4.3±0.4	23.99		<0.05
2h PBG (mmol/l)	6.3±0.6	5.1±0.5	21.70		<0.05
FINS (mU/l)	13.01±2.32	9.46±1.78	10.28		<0.05
TG (mmol/l)	2.59±0.23	1.11±0.11	49.04		<0.05
TC (mmol/l)	4.9±0.4	4.2±0.3	11.86		<0.05
HDL (mmol/l)	1.01±0.12	1.42±0.11	21.36		<0.05
LDL (mmol/l)	2.93±0.21	2.09±0.19	25.15		<0.05
ALT (U/l)	85.4±4.89	63.9±3.45	30.41		<0.05
AST (U/l)	54.14±4.56	35.21±3.21	28.73		<0.05
IL-2 (pg/l)	34.92±4.03	22.33±4.56	10.43		<0.05
IL-6 (IL-2)	45.32±4.01	32.53±3.09	9.78		<0.05
CRP (mg/l)	13.43±3.98	7.31±1.01	7.89		<0.05

two groups (with or without steatosis). The results showed that the age, sex, and disease course between two groups showed no significant difference. However, in chronic hepatitis B patients with steatosis, FBG, 2h PBG, FINS, TG, TC, IL-2, IL-6, CPR, LDL, ALT, and AST were significantly higher than those in chronic hepatitis B patients without steatosis ($p<0.05$) (Table I).

Comparisons of Steatosis, Liver Function, and Glucolipid Metabolism Indicators Among Patients With Different Inflammations

Based on the level of C-reactive protein (CRP) (8 mg/L), in the abnormal group, fatty degeneration grade was significantly increased compared to that in the normal group, on account for the amount of F1 patients was significantly fewer than that in the normal group ($p<0.05$) (Table II). Moreover, liver function indicators (ALT and AST) and glucolipid metabolism indicators (FBG, 2h PBG, FINS, TG, TC, HDL, and LDL) were significantly decreased in the abnormal group, as the level of C-reactive protein (CRP) was higher than 8 mg/L ($p<0.05$) (Table II).

Comparisons of Steatosis, Glucolipid Metabolism, and Inflammation Indicators Between Patients With Normal Liver Functions and Abnormal Liver Functions

According to the level of AST (>40 U/L), the patients with steatosis were further divided into the normal liver function group and the abnormal liver function group. In a similar fashion, fatty degeneration grade in the abnormal liver function group was also significantly elevated compared to that in the normal liver function group, due to the increasing number of F2-3 patients in the ab-

Table II. Comparisons of steatosis, liver function and glucolipid metabolism indicators among patients with different inflammations.

Item	Normal group	Abnormal group	*t*	X^2	*p*
F1 group	35	5		18.58	<0.05
F2-F3 group	13	20		18.58	<0.05
ALT (U/l)	87.2±5.6	64.8±6.0	15.48		<0.05
AST (U/l)	57.21±5.75	36.97±2.98	19.87		<0.05
FBG (mmol/l)	6.2±0.7	4.5±0.4	13.23		<0.05
2h PBG (mmol/l)	6.4±0.3	5.2±0.5	8.09		<0.05
FINS (mmol/l)	14.21±3.2	9.17±2.1	45.91		<0.05
TG (mmol/l)	2.63±0.19	1.02±0.11	12.82		<0.05
TC (mmol/l)	5.2±0.5	4.0±0.3	10.95		<0.05
HDL (mmol/l)	1.05±0.10	1.32±0.10	8.76		<0.05
LDL (mmol/l)	3.05±0.23	2.01±0.17	21.92		<0.05

Table III. Comparisons of liver functions, inflammations and glucolipid metabolism indicators between two groups of patients.

Item	Patients with abnormal liver functions	Patients with normal liver functions	*t*	X^2	*p*
F1 group	13	18		13.57	
F2-F3 group	35	7		13.57	
FBG	6.3±0.5	4.2±0.3			
2h PBG	6.4±0.6	5.0±0.4			
FINS	14.21±2.43	9.42±3.09			
TG	2.67±0.2	1.10±0.1			
TC	4.7±0.4	4.1±0.3			
HDL	1.00±0.1	1.32±0.1			
LDL	2.98±0.21	2.11±0.20			
IL-2 (pg/l)	35.01±4.33	21.03±4.06	11.03		<0.05
IL-6 (IL-2)	46.82±4.11	33.73±3.79	9.08		<0.05
CRP (mg/l)	13.83±3.68	7.21±1.11	7.29		<0.05

normal liver function group (p<0.05) (Table III). Notably, except for HDL, the levels of FBG, 2h PBG, FINS, TG, TC, LDL, IL-2, IL-6, and CRP in the abnormal liver function group were statistically increased compared to those in the normal function group (p<0.05) (Table III).

Correlations of Fatty Degeneration Grade With Glycolipid and Liver Functions

We then performed the correlation analysis of fatty degeneration grade with liver function indicators. Of note, the steatosis was positively correlated with indicators, including the blood glucose indicator of FBG (r=0.509, p<0.05), the liver function indicator of AST (r=0.602, p<0.05), the blood lipid indicator of TG (r=0.740, p<0.05), and the inflammatory factor of CRP (r=0.882, p<0.05) (Figures 1-4).

Logistic Regression Analysis of Risk Factors Predicting Steatosis

Logistic regression analysis was conducted to determine the risk factors predicting steatosis. Except for factors of age, gender, and disease course, body mass index (BMI), 2h FBG, TG, TC, HDL, LDL, AST, ALT, and inflammatory factors served as independent predictive value for steatosis in chronic hepatitis B patients (p<0.05) (Table IV).

Discussion

Patients with chronic hepatitis B tend to be attacked by steatosis lesions and often suffer from obesity[10-12]. The steatosis gives rise to the increased risk of impairment in the liver and other organs, thus affecting individual's health[13-15]. The

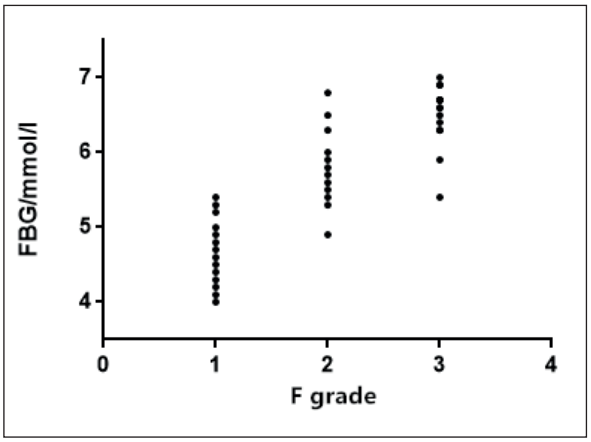

Figure 1. Analysis of correlation between steatosis and FBG. F grade, that is, fatty degeneration grade, is positively correlated with FBG (r=0.509, p<0.05).

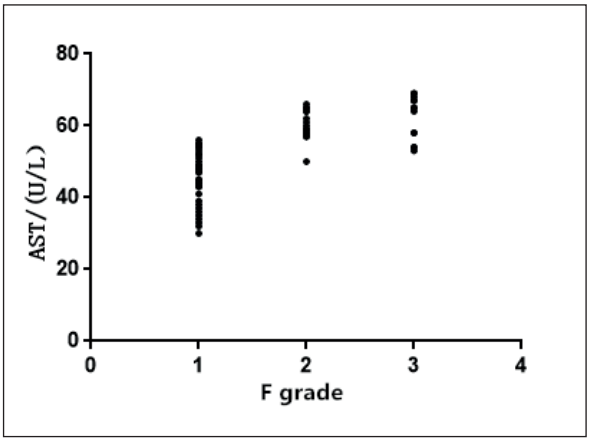

Figure 2. Analysis of correlation between steatosis and AST. F grade, that is, fatty degeneration grade, is positively correlated with AST (r=0.602, p<0.05).

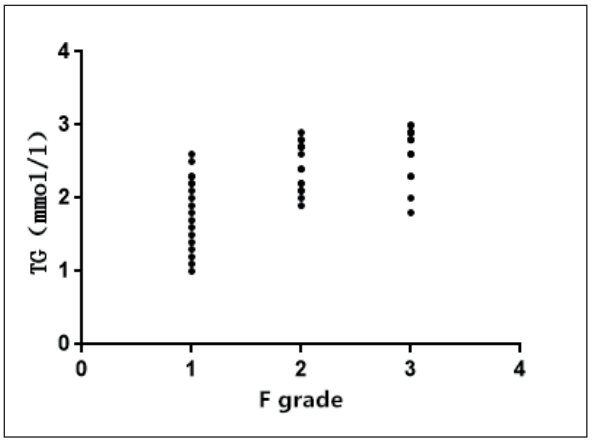

Figure 3. Analysis of correlation between steatosis and TG. F grade, that is, fatty degeneration grade, is positively correlated with TG (r=0.740, p<0.05).

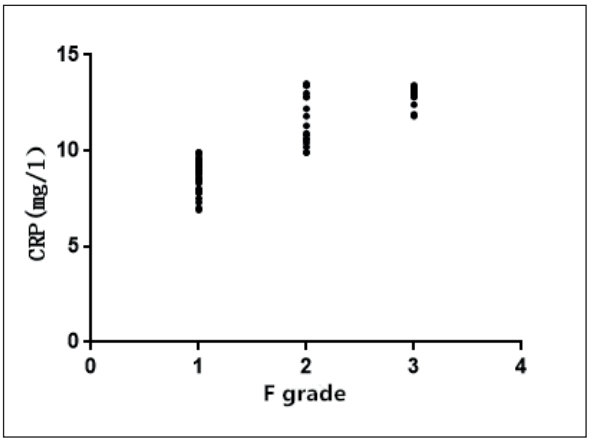

Figure 4. Analysis of correlation between steatosis and CRP. F grade, that is, fatty degeneration grade is positively correlated with CRP (r=0.882, p<0.05).

clinical statistics has shown that among chronic hepatitis B patients with steatosis, the obese population occupies the majority[16]. In the patients with steatosis, excessive fatty acid is commonly secreted in peripheral adipose tissues, and the amount of fatty acid absorbed by the liver can be also increased correspondingly, leading to the deposit of fatty acid in liver tissues. As a result, TG synthesis speeds up, and the steatosis in patients is exacerbated when TG is increased to a certain degree in liver cells[17,18].

The liver is associated with glucolipid metabolism. The chronic hepatitis B can affect the secretion of insulin in patients, which causes insufficient production of insulin after meal. Therefore, the content of postprandial blood sugar cannot be normally controlled and regulated. The increase of blood sugar, the resistance of blood insulin in liver and decrease blood glucose intake were found in patients' liver[19,20]. It was found that among hepatitis B patients, the inflammatory grades of patients with moderate and severe steatosis were significantly severer than those with mild steatosis. Besides, studies[21,22] has revealed that the hepatic steatosis is negatively correlated with *in vivo* serum adiponectin.

Table IV. Logistic regression analysis of risk factors predicating steatosis.

Item	p	OR	95%CI
Age	0.727	0.927	0.131, 3.564
Gender	0.692	1.021	0.128, 5.76
Course of disease	0.701	1.011	0.291, 6.544
BMI	0.042	2.321	0.301, 7.659
2h PBG	0.031	1.921	0.123, 9.876
FINS	0.029	5.219	0.126, 10.032
TG	0.032	4.259	0.134, 6.789
TC	0.041	1.573	0.142, 5.986
HDL	0.021	0.523	0.154, 8.765
LDL	0.019	1.792	0.186, 7.893
ALT	0.035	2.321	0.542, 7.843
AST	0.042	1.979	0.876, 6.432
IL-2	0.035	4.542	0.575, 9.874
IL-6	0.032	4.021	0.654, 10.765
CRP	0.021	3.984	0.543, 8.965

According to our data, in chronic hepatitis B patients with steatosis, the glycolipid indicators, liver function indicators, and inflammatory factors were higher than those in patients without steatosis. This indicated that the elevation of blood glucose and lipid levels in patients with steatosis caused liver function impairment and exacerbated inflammations. The correlations between the inflammations, glycolipid, and liver functions were analyzed for chronic hepatitis B patients with steatosis, and it was found that steatosis was positively correlated with FBG, AST, TG, CRP. The therapy of chronic hepatitis B remains a complicated process, which is affected by a variety of factors[23]. Current finding[24] showed a multitude of indicators were closely related to the progression of chronic hepatitis B. Based on the cohort of chronic hepatitis B patients with steatosis, distinct indicators were analyzed and identified, although a further study on a larger group of patients still requires to evaluate the clinical value for diagnosis and treatment.

Conclusions

We demonstrated that steatosis resulted in the alternation of glucolipid metabolism, liver functions, and inflammations levels, among which, the correlated indicators can be fully considered to effectively prevent, diagnose, and treat steatosis in chronic hepatitis B patients.

Conflict of Interests:

The Authors declare that they have no conflict of interests.

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